REMARKS

Claims 1-30 are pending in the application. Claims 2-8, 10-12, 14, 16-18, and 25-30 have been cancelled by this amendment. Therefore, claims 1, 9, 13, 15, and 19-24 are at issue.

The claims have been amended to conform in scope to applicant's elected invention. Claims 2-8, 10-12, 14, 16-18, and 25-30 have been cancelled without prejudice to filing divisional applications directed to the subject matter of these claims. Claim 1, the sole independent claim, has been amended to more clearly recite a therapeutic treatment for a human suffering from Alzheimer's disease and to incorporate the features of originally filed claim 7, i.e., the elected mixed ET_A/ET_B endothelin antagonists of Appendix B. Claim 1 also has been amended to incorporate the features of originally-filed claim 25 into claim 1 and recite treatment of a human.

Claim 9 has been amended to recite applicant's elected specie of endothelin antagonist. Claim 13 has been amended to recite applicant's elected specie of second therapeutic agent. Claims 15 and 19-24 have been amended to correct a claim dependency and provide a proper recitation "cholinesterase inhibitor" in place of a "second therapeutic agent".

Independent claim 1 is now directed to a therapeutic method of treating an human suffering from Alzheimer's disease by administering a therapeutically effective amount of a claimed endothelin antagonist. The endothelin antagonist can be administered alone, or in combination with a cholinesterase inhibitor, as set forth in claims 13-15 and 19-24.

Prior to addressing the issues raised in the Office Action, applicant would like to clarify the claimed invention for the examiner. The present invention is *not* directed to a cure for Alzheimer's disease. A person suffering from Alzheimer's disease will not be freed from the disease by the present method. The present method *does* treat adverse effects or symptoms resulting from Alzheimer's disease. As discussed more fully below in connection with a rejection under 35 U.S.C. §112, first paragraph, the present method addresses the issue of a reduced blood flow to the brain that is caused by Alzheimer's disease. The present

method overcomes the vasoconstriction associated with Alzheimer's disease and improves a blood flow in the brain. This difference between cure and treatment must be kept in mind when considering the patentability of the presently claimed method.

In the Office Action, the examiner asserts that the declaration is defective for failing to identify the application number and filing date. The examiner is directed to MPEP §602 VI (August, 2006, page 600-35), wherein it is stated that an application number is desired, but *not* essential. The previously filed declaration adequately identifies the specification to which it is directed because the declaration includes a title of the invention, a filing date, an attorney docket number (page 2), the identity of the priority application, and the name and address of the inventor. Accordingly, the examiner's objection is unfounded. However, to facilitate prosecution, applicant transmits a substitute declaration, including an application number, concurrently with this amendment. The examiner's objection therefore has been overcome.

The examiner also has issued two rejections under 35 U.S.C. §112, first paragraph. In the first rejection, all pending claims stand rejected under 35 U.S.C. §112, first paragraph, based on the contention that the specification does not reasonably provide enablement for the full scope of the claims. In the second rejection, all pending claims stand rejected under 35 U.S.C. §112, first paragraph, based on the contention that the specification is not enabling for a prophylactic treatment of Alzheimer's disease, i.e., preventing the disease. It is submitted that these rejections are in error or have been overcome, and should be withdrawn.

With respect to the second rejection under 35 U.S.C. §112, first paragraph, the originally-filed claims never recited a prophylactic treatment. For example, the term "prevent" was never recited in the claims. Importantly, the original claim recited "administered to a mammal in need thereof", thereby indicating that the mammal already suffers from Alzheimer's disease. If prevention was contemplated, the phrase "in need thereof" would not have been present in the claim.

However, to facilitate prosecution, applicant has amended independent claim 1 as suggested by the examiner at page 22 of the Office Action in order to clarify that the

method does not encompass a preventative treatment. Accordingly, it is submitted that this rejection of claims 1, 9, 13, 15, and 19-24 under 35 U.S.C. §112, first paragraph, has been overcome and should be withdrawn.

With respect to the first rejection under 35 U.S.C. §112, first paragraph, i.e., non-enablement for the full scope of the claims because a skilled artisan would require undue experimentation to fully practice the claimed invention, the examiner relies upon the eight *Wands* factors to support the rejection.

Overall, the examiner bases this rejection on two issues. First, that the specification is not enabling for treating Alzheimer's disease or all dementias of vascular origin, in any mammal. Second, the specification lacks enablement for treating Alzheimer's disease or all dementias of vascular origin using any mixed ET_A/ET_B endothelin antagonist. It is submitted that this rejection has been overcome and should be withdrawn.

Prior to addressing each of the eight *Wands* factors, the examiner should note that the claims now recite a treatment of a human suffering from Alzheimer's disease, not dementias of vascular origin. The claims also have been amended to recite the specific endothelin antagonists originally recited in claim 7, and, in claim 9, to recite a specific endothelin antagonist.

In addition, the examiner is reminded that MPEP §2164 *et seq.* states that the enablement requirement of 35 U.S.C. §112, first paragraph, requires that the specification describe how to make and how to use the claimed invention *to one skilled in the art*. The standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is *undue* or *unreasonable*. In *re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed Circ. 1988). Further, the test of enablement is whether one reasonably skilled in the art could make and use the invention from the disclosure in the patent specification *coupled with the information known in the art* without *undue* experimentation. A patent need not teach, and preferably omits, what is well known in the art.

The *Wands* factors were not conceived in a vacuum, but in relation to a substantial body of case law, which also must be considered when applying the eight *Wands* factors. In particular, an examiner's requirement that applicant's claims be limited to a specific embodiment disclosed in the specification is like that reversed by the CCPA in *Application of Johnson*, 558 F.2d 1008, 1017 (CCPA 1977), wherein the Court said:

> "The PTO would limit appellants to claims reciting a sigma* value of at least 0.7. This view is improper because it requires the claims to set forth the practical limits of operation for the invention and it effectively ignores the scope of enablement provided by the specification as a whole". (Emphasis added)

As the CCPA pointed out in *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46,48 (CCPA 1974), 35 U.S.C. §112 requires only a disclosure *in the specification* (i.e., not the claims) "sufficient to enable practice of the invention by one skilled in the art, taking into account obvious modifications...". The court also said:

> "It is not the function of the *claims* to specifically exclude other possible inoperative substances"; citing authority (Emphasis not ours).

Similarly, in *American Anode Inc. v. Lee-Tex Rubber Products Corporation*, 136 F.2d 581, 585 (7th Circ. 1943), the Court said:

> "There is no doubt that a patentee's invention may be broader than a particular embodiment shown in his specification. A patentee is not only entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims which define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 55 S.Ct. 279, 79 L.Ed. 721".

The Court of Appeals for the Federal Circuit has upheld and sustained this line of reasoning in regard to 35 U.S.C. §112. For example, in *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 1576 (Fed. Cir. 1984), the CAFC stated:

> "The district court rejected DuPont's arguments of "overly broad", "overclaiming", and "non-enablement", and its argument that the broad scope of the claims is not supported by the limited disclosure present. In essence, those arguments are one: the '978 disclosure does not enable one of ordinary skill in the art to make and use the claimed invention, and hence, the claimed inventions is invalid under 35 U.S.C. §112, ¶ 1.

To be enabling under §112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. Raytheon Co. v. Roper Corp., 724 F.2d at 960, 220 USPQ at 599. That some experimentation is necessary does not preclude enablement; the amount of experimentation, however, must not be unduly extensive. See e.g., *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983), cert. denied, ---U.S.---, 105 S. Ct. 172, 83 L.Ed.2d 498, 503, 190 USPQ 214, 218 (CCPA 1976)...".

In addition, the Court stated in In re Wands, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988):

"Enablement is not precluded by the necessity for some experimentation such as routine screening. However, *experimentation* needed to practice the invention must not be undue experimentation. "the key word is 'undue' not 'experimentation'."[1]

The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* [448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018 [172 USPQ 257] (1972)]. The test is not merely quantitative, *since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.*"[2] (Emphasis added)

Also, in *U.S. v.* Telectronics, *Inc.*, 8 USPQ 2d 1217, 1223-1224 (Fed Cir. 1988), the court stated:

"...Finally, the emphasis by the district court on the time and cost of such studies is misplaced. While these factors may be taken into account, in the circumstances of this case we are unpersuaded that standing alone they show the experimentation to be excessive. The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d. 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 107 S.Ct. 1606 (1987).

Since one embodiment is admittedly disclosed in the specification, along with the general manner in which its current range was ascertained, we

[1] *In re Angstad*, 537 F2Q 498,504 (CCPA 1976).
[2] *Ex Parte Jackson*, 217 USPQ 804,807 (Pt. Bd. App. 1982).

> are convinced that other permutations of the invention could be practiced by those skilled in the art without undue experimentation. See *SRI Int'l v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577, 586 (Fed Cir. 1985) (the law does not require an applicant to describe in his specification every conceivable embodiment of the invention); *Hybritech Inc.*, 802 F.2d at 1384, 231 USPQ at 94 (the enablement requirement may be satisfied even though some experimentation is required)..."

An applicant is entitled to claims commensurate in scope with his disclosure. An examiner's attempt to limit applicant to the embodiment specifically disclosed in the specification has been consistently reversed by the courts. For example, in *In re Goffe*, 191 USPQ 429, 431 (CCPA 1976), the CCPA stated:

> "For all practical purposes, the board would limit appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently-issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts. See *In re Fuetterer*, 50 CCPA 1453, 1462, 319 F.2d 259, 265, 138, USPQ 217, 223 (1963)."

Furthermore, the CAFC stated in *Rohm & Haas Co. v. Dawson Chem. Co.*, 557 F. Supp. 739, 217 USPQ 515 (S.D. Tex. 1983), rev'd on other grounds sub nom. *Rohm & Haas Co. v. Crystal Chem. Co.*, 722 F.2d 1556, 220 USPQ 289 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984):

> "Once this invention was conceived,...the inventors embarked on a series of field tests in 1957 which established selectivity in post-emergence application with a number of crops...Under the circumstances, Rohm & Haas *was not required to limit its 1958 application to the precise crops where selectivity had at that time been demonstrated. Such a requirement would discourage an inventor from disclosing and teaching his discovery for the public's benefit until all screening had been completed, in contravention to the guiding principles underlying §112*". (Emphasis added)

Turning to the eight *Wands* factors, it can be seen that applicant has provided sufficient guidance to persons skilled in the art to practice the claimed invention, and has enabled the *presently claimed* invention over the full scope of the claims.

(1) Nature of the Invention and Scope of the Claims

The invention now is clearly directed to a method of treating a human suffering from Alzheimer's disease. The examiner objects to the claims because the claims originally were directed to treating mammals for all dementia of vascular origin. The amended claims overcome the contentions of the examiner with respect to the scope of the diseases treated by the present method, and the mammals treated by the present method.

The examiner also objects to the scope of the claims relating to the identity of the endothelin antagonist. The claims no longer recite already known and unknown endothelin antagonists as contended by the examiner, but specifically recite the mixed ET_A/ET_B antagonists originally recited in claim 7, and claim 9 recites a single endothelin antagonist.

The examiner's arguments relating to the structure of the compounds recited in present claim 1 (and in Appendix B) are irrelevant. The examiner's contentions arguably would be correct *if* a specific activity of *new* compounds having a diverse structure were at issue. This is not the case. The compounds recited in claim 1 are *known* compounds, and have been identified by persons skilled in the art as endothelin antagonists. In fact, a reference *cited by* the examiner, i.e., the Wu publication, shows that persons skilled in the art know, recognize, and classify these claimed compounds as mixed ET_A/ET_B endothelin antagonists. Thus, the examiner's statement that compound 46 and compound 48 have different structures and "are not expected to have similar chemical reactions or biochemical functions" to *those skilled in the art* has no basis and is incorrect. See cited Wu publication identifying and classifying endothelin antagonists. The reference clearly refutes the examiner's contentions.

It is applicant's position, therefore, that the claimed endothelin antagonists are well known in the art, and that their activity with respect to endothelin antagonism also is well known to persons skilled in the art even though their chemical structures differ. This is illustrated by the examiner's own cited art. Accordingly, there is sufficient guidance provided to persons skilled in the art to practice the invention, and rather than undue experimentation,

no experimentation arises because *all* claimed compounds are *known* in the art as mixed ET_A/ET_B endothelin antagonists.

Furthermore, the examiner is directed to claim 1, which recites *specific* endothelin antagonists. Claim 9 recites a single endothelin antagonist. The scope of the claimed endothelin antagonist therefore is not unduly broad. In fact, the examiner in a prior restriction requirement considered the claimed endothelin antagonists to be sufficiently close in structure and/or activity to be grouped together as a single invention. An extension of this reasoning means that they are expected to perform similarly, especially in view of the fact that *each* compound has been identified by persons skilled in the art as mixed ET_A/ET_B endothelin antagonists.

(2) State of the Art

The examiner states that Alzheimer's disease is a complex disease, with a yet unknown complete etiology, and that treatments are still unsatisfactory. After citing publications regarding a lack of an animal model, etc., the examiner concludes that "the state of the art indicates that it is not known whether the decline of neurotoxicity of Beta-amyloid *in vitro* is predicative of the treatment of the Alzheimer's disease in a patient". The examiner relies upon a May publication in making this statement.

The examiner asserts that no animal model for Alzheimer's disease (AD) exists for use by persons skilled in the art in investigating treatments for the diseases. If taken to be a true statement, what is left except for *in vitro* testing? A prominent feature of AD is the presence of extracellular neuritic plaques that have a β-amyloid (Aβ) at their core. See May publication. Therefore, observing a reversal of the effects of Aβ neurotoxicity is an excellent *in vitro* test in determining a treatment for AD.

Furthermore, the examiner misconstrues the May publication. The May publication, in the abstract, clearly states that "[T]he amyloid-β (Aβ) peptide remains central to many therapeutic approaches currently under development for Alzheimer's disease (AD)". May, therefore, clearly teaches Aβ investigations are important in an AD treatment. The publication then goes on to discuss two specific treatments for which the results are

ambiguous, i.e., inhibition of enzymes leading to the production and accumulation of Aβ. In effect, the publication is directed to, and limited to, attempts at limiting the production and/or accumulation of Aβ, which is expected to lead to a benefit. It is *these specific attempts* that lead to ambiguous results.

The May publication also recognizes that *in vitro* models "have been established emulate at least some aspects" of Aβ pathology. The reference also states that "evidence continues to mount which supports "the Aβ hypothesis for AD". See May reference, Summary, page 18.

In addition, as discussed above, the present invention addresses the treatment of AD differently from that of the May reference, making the ambiguity of that study irrelevant. The present invention does not effect either Aβ generation or an accumulation of Aβ. The present invention is directed to treating AD by increasing blood flow to the brain, and thereby alleviate adverse effects of AD. The present invention is *not* directed to a cure for the underlying AD condition, but is directed to treating events caused by the disease and symptoms of the disease. Such treatments are well known in the art as "functional antagonism", and are used in the control and treatment of numerous diseases and conditions.

May is attempting to reduce the production/accumulation of Aβ and cure AD. The present invention is not. The present invention is directed to overcoming the vasoconstrictive activity associated with Aβ, and therefore allow a more normal blood flow in the brain. The administration of an endothelin antagonist to an Alzheimer's patent is *not* to eliminate or reduce Aβ, but to improve blood flow in the brain. In effect, the present invention counters a biological activity, which result from the presence of Aβ, i.e., reducing the adverse effects associated with vasoconstriction attributed to AD and improving blood flow in the brain.

The examiner appears to be stating a rejection under 35 U.S.C. §101, i.e., the invention is inoperative or incredible because a decline in Aβ neurotoxicity is not known to be predictive of AD treatment. That is not the rejection here. Applicant clearly has stated a utility, based on sound and accepted scientific principles, with test results to demonstrate that utility. What is at issue is whether there is an undue burden on persons skilled in the art to

practice the claimed invention. The fact is that little experimentation is required, i.e., a specific disease treated by specific, known compounds of known activity.

In fact, persons skilled in the art support the basis of the present invention, i.e., that an endothelin antagonist is useful in the treatment of AD by increasing blood flow to the brain of an individual suffering from AD. As known in the art, the most prominent feature of AD is the extracellular neuritic plaques, which have at their core β-amyloid (Aβ), cleaved from amyloid precursor protein (APP). Aβ has been suggested to have a significant vasoactive role (F. Crawford et al. (1998) *FEBS Lett* 436(3):445-8). In addition, it has been reported that increasing concentrations of Aβ can contribute to AD pathology by inducing microvascular vasoconstriction and reducing cerebral blood flow, resulting in hypoperfusion and ischemia (L.D. Thomas (1996) *Int J Nurs Pract* 2(1):29-32). In addition, a decrease in cerebral blood flow has been confirmed in senile dementia of Alzheimer's type (W.J. Jugust et al. (1987) *Annals of Neurology* 44:258-262). The concept that AD is primarily an ischemic type, rather than degenerative type, of brain disease also is gaining strong support (E. Niedermeyer (2007) *Clin EEG Neurosci* 38(1):55-6). Recently, using the claimed endothelin antagonist, bosentan, it was demonstrated that the endogeneous endothelin system represents a key factor in the pathogenesis of endothelial dysfunction associated with AD (A. Elesber et al. (2006) *Neurobiol Aging* 27(3):446-50). These studies indicate that the present invention is based on sound scientific principles, not outrageous or incredible theories.

The present claims recite a specific disease and specific compounds, and *in vitro* tests are disclosed for use by persons skilled in the art. Although the prior art may not be dispositive with respect to a decrease in Aβ being predictive of an AD treatment, that is not germane to the *present* invention. There is no unpredictability in the present claims based on the prior art. The art may be unsettled on how to best investigate AD treatments, but the claims recite specific compounds for treating a specific disease.

The examiner's comments relating to the different structure of the claimed compounds is irrelevant for the reasons stated above. All are *known* endothelin antagonists, of the same type and activity, regardless of structure. The relative efficacy of the compounds may differ, but such differences are readily determined by tests set forth in the specification. Furthermore, any differences in efficacy do not relate to patentability because all are known

mixed ET_A/ET_B antagonists, operate by the same mechanism, and therefore are expected to perform similarly in reducing Aβ toxicity. Differences in efficacy between compounds are well known in the art, and are *not* an issue under 35 U.S.C. §112, first paragraph, which looks to undue experimentation. Also, see examiner's cited reference WO 01/17976, Table 1, which reports endothelin antagonists of a general structure having different efficacies.

(3) Relative Skill in the Art

The relative skill in the art is *quite* (not "fairly") high, i.e., a medical or advanced degree. Accordingly, persons skilled in the art are well aware that *all* the claimed compounds are endothelin antagonists that operate by the same mechanism. See Wu publication. Furthermore, the claimed compounds have been so classified as mixed ET_A/ET_B endothelin antagonists by these persons skilled in the art.

(4) Predictability of the Art

The predictability of the art is discussed above in connection with the state of the art. Although the therapeutic art may be unpredictable, the May reference relied upon by the examiner concedes that "numerous *in vitro* studies document the neurotoxic and proinflammatory properties of Aβ peptide". Furthermore, although May reports that inhibiting Aβ peptide generation and accumulation yielded unambiguous results, this in no way translates to results provided by administration of an endothelin antagonist. The described treatments in May may be ambiguous because they are the *wrong* treatments, and are directed to curing AD. The present invention, unlike May and as discussed above, is *not* directed to reducing Aβ production/accumulation, and not curing AD, but to improving blood flow in the brain.

There is no unpredictability in how a claimed endothelin antagonist works. All claimed endothelin antagonists are *known* and tested compounds that persons skilled in the art have identified and classified as mixed ET_A/ET_B endothelin antagonists. Accordingly, no unpredictability can be attributed to how a claimed endothelin antagonist will act. The claimed endothelin antagonists have a reported activity similar to the tested endothelin antagonist. Therefore, persons in the art can reasonably expect the recited endothelin

antagonists to perform like the endothelin antagonist used in the disclosed tests. Accordingly, the examiner's statement that each embodiment must be assessed for physiological activity because of unpredictability is incorrect in this case. All claimed compounds *have* been tested for physiological activity, and classified together by persons skilled in the art.

Some of the claimed endothelin antagonists are undergoing clinical testing because of their demonstrated endothelin antagonism. Bosentan, as recited in claim 9, is a commercial drug based on its endothelin antagonism. Again, this illustrates that there is *no* unpredictability in how a claimed endothelin antagonist works.

(5) Guidance of the Specification/(6) Working Examples

In view of the specification, and for all of the reasons discussed above, it is submitted that applicant, in the present specification, provides sufficient guidance and direction to allow a person skilled in the art to make and practice the claimed invention. The specification fully and clearly describes the features of the claimed method. A person of ordinary skill in the art is capable of testing claimed endothelin antagonists as an AD treatment. Accordingly, as expressed in *In re Wands*, the present specification provides a person of ordinary skill in the art sufficient guidance with respect to the direction of the experimentation, and the screening experimentation is routine.

The examiner appears either consciously or inadvertently to have followed a practice specifically condemned by the CCPA in *In re Borkowski and Van Venrooy*, 164 USPQ 642, 645 (CCPA 1970) where the Court said:

> "The examiner's approach to determining whether appellants' claims satisfy the requirements of §112 appears to have been to study appellants' disclosure, to formulate a conclusion as to what he (the examiner) regards as the broadest invention supported by the disclosure, and then to determine whether appellants' claims are broader than the examiner's conception of what 'the invention' is. We cannot agree that §112 permits of such an approach to claims.

The courts have consistently reversed rejections such as the present 35 U.S.C. §112, first paragraph, rejection. Applicant has sufficiently described the endothelin

antagonists to enable a person skilled in the art to make and use the claimed invention. The examiner's requirement to limit applicant to a specific compound is an attempt to preclude applicant from obtaining protection commensurate in scope with the invention described in specification as a whole.

The present invention lies in the administration of an endothelin antagonist in a method of treating AD. The invention does *not* lie simply in a particular endothelin antagonist. To so limit the applicant would deprive applicant of the full scope of this invention and defeat a primary purpose of patent system, which is to promote early disclosure of an invention before all permutations of the invention are investigated and perfected.

Applicant has claimed a reasonable extension of the compound tested by reciting endothelin antagonists classified together by persons skilled in the art and that operate by the same mechanism of action as the compound used in the tests. The specification teaches endothelin antagonists, and that administration of an endothelin antagonist increases blood flow constricted by the presence of Aβ. Accordingly, the specification and tests, coupled with known information in the art, provide sufficient guidance for persons skilled in the art to make and use practice the claimed invention without undue experimentation.

In particular, the examiner contends that the specification "does not disclose that drugs that act as endothelin antagonists are known in art to be useful in the treatment of Alzheimer's disease". Of course not! If so, there would be *no* invention. It is applicant that made this discovery. In addition, the inventor *did* teach how endothelin antagonists are correlated to an Alzheimer treatment, i.e., a reduction of the vasocontrictive effects of Aβ, which is directly correlated to AD, by increasing blood flow.

The examiner admits that data is provided showing the Aβ increases the endogenous concentration of ET-1, which leads to vasoconstriction, and that administration of an endothelin antagonist causes a rebound in blood flow. The specification therefore contains tests in support of the claimed invention *and* provides sufficient guidance to a person skilled in the art to practice the full scope of the presently claimed invention.

As to the argument relating to functional language, the claims now recite specific compounds known in the art as endothelin antagonists. Accordingly, these arguments of the examiner are moot.

The tests set forth in the specification are well established protocols used by persons skilled in the art. The examiner is directed to the case law discussed above, which clearly dictates that all that is required in the specification is sufficient guidance to allow persons skilled in the art on how to practice the invention. In fact, not even one example is required.

Applicant has provided such guidance, i.e., tests that demonstrate the utility provided by the presently claimed invention, and how persons skilled in the art can perform standard, routine testing of an endothelin antagonist in the treatment of Alzheimer's disease *without* undue experimentation. Persons skilled in the art simply have to test an endothelin antagonist, as claimed, following the procedures set forth in the specification, to determine the relative effectiveness of the treatment of controlling Alzheimer's disease. This cannot be considered undue experimentation under the case law discussed above.

Applicant has provided tests wherein endothelin antagonists can reverse vasoconstriction attributed to Aβ. The tests utilize standard protocols used in art. In addition, applicant has disclosed *and claimed* additional endothelin antagonists that operate *by the same or related mechanism* as the endothelin antagonist used in the test. Persons skilled in the art are well aware of a variety of endothelin antagonists, and these compounds have been identified by researchers as endothelin antagonists, are expected to perform similarly to the endothelin antagonists of the examples. Further, the examiner has provided no rationale supporting any doubts regarding the truth or accuracy that a claimed endothelin antagonist would not operate like the endothelin antagonist of the test.

In addition, it is not incumbent upon the applicant to provide test data for each endothelin antagonist to support the claimed invention. Applicant must only provide sufficient guidance to persons skilled in the art to practice the claimed invention without undue experimentation. It is irrelevant that some experimentation may be necessary. Applicant has met his burden by showing that the therapeutic effects of an endothelin

antagonist for use in a treatment of AD, both in the disclosure of the specification and in the tests therein.

(7) The Quantity of Experimentation Necessary

The examiner overstates the experimentation necessary to practice the claimed invention. Envisioning a specific endothelin antagonist is not burdensome in view of the fact that *specific* endothelin antagonists are well known and claimed.

With respect to envisioning a pharmaceutical carrier, a dosage, duration of treatment, route of treatment, toxicity, etc., these aspects of the treatment are *optimizing* the claimed invention, and very well can be separate inventions. Requiring applicant to conclusively include such parameters in the specification is contrary to the case law discussed above. In addition, the claimed endothelin antagonists are not *new* compounds, some are undergoing clinical testing, and at least one is a commercial drug. Therefore, these parameters are *known* to persons skilled in the art, and essentially *no* burden is placed on persons skilled in the art.

The examiner apparently is requiring a FDA approved and commercial embodiment to be developed prior to filing a patent application, and is extending the "required" experimentation to include toxicity, adverse effects, and dosages. Such experimentation is *not* directed to supporting applicant's claimed invention. The examiner also is directed to *In re Brana*, 51 F.3d 1560 (1994) stating that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws." Accordingly, it is *not* incumbent on applicant to demonstrate that a therapeutic agent is a safe or fully effective drug for humans. See MPEP, §2107.03, page 2100-36 (August, 2006).

As stated above, bosentan, which is recited in claim 9, is a commercial drug that has been on the market for several years. Other endothelin antagonists are in various stages of clinical trials. Therefore, the examiner's comments regarding toxicity, dosage, etc. have already been addressed by persons skilled in the art.

Regardless, the type of experimentation described by the examiner is routine and is of the type of standard experimentation conducted for essentially any drug or medical

treatment, and typically *after* patenting when optimizing a drug or method for FDA approval and commercialization. Again, please note the case law discussed above, especially the discussion of *U.S. v. Telectronics* at page 15 above.

Further, applicant is not seeking a hunting license. Applicant has provided an enabling disclosure, not vague information or general ideas that may or may not be workable. Applicant has not provided merely theory. Applicant teaches that Aβ is prevalent in AD and promotes ET-1, which leads to vasoconstriction. Accordingly, applicants' invention is to administer an endothelin antagonist to overcome vasoconstriction and provide a treatment for AD. This is a scientifically concrete conclusion, supported by persons skilled in the art as set forth above, not some unbelievable theory. Furthermore, applicant has provided concrete tests showing the benefits of the claimed invention, together with sufficient guidance to practice the claimed invention.

It also must be noted that the specification contains tests showing an endothelin antagonist that is useful in the treatment of AD. When coupled with knowledge in the art, *routine* experimentation with the other claimed endothelin antagonists by procedures known in the art, and disclosed in the specification, will reveal the ability of the other claimed endothelin antagonists to treat AD. The tests of the specification clearly show that the protocols used in such experimentation are routine and unburdensome.

As for the quantity of experimentation necessary to practice the claimed invention, the routine experimentation to optimize administration of an endothelin antagonist is insignificant. Given the highly developed state of the art and the high level of skill in the art, any of a number of straightforward assays may be identified as suitable under a given set of circumstances. Experimentation in the form of conducting a simple assay where indicated, coupled to routine experimentation to optimize delivery, does not signal a significant quantity of required experimentation.

The nature of the invention, i.e., methods of treating AD by administering specifically claimed compounds, also favors a conclusion that the pending claims are enabled by the specification. It should be further noted that the state of the art and level of skill in the art lead to a conclusion that the claims are enabled. The subject matter of the application

coupled to routine experimentation to optimize delivery, does not signal a significant quantity of required experimentation.

The nature of the invention, i.e., methods of treating AD by administering specifically claimed compounds, also favors a conclusion that the pending claims are enabled by the specification. It should be further noted that the state of the art and level of skill in the art lead to a conclusion that the claims are enabled. The subject matter of the application shows that the state of the art is advanced, and medical researchers and practitioners are widely recognized as being highly educated and containing a high level of skill. Endothelin antagonists are known to persons skilled in the art, thus there is no undue experimentation with respect to the identity of the compounds used in the claimed method.

Finally, the pending claims are precisely tailored to the invention disclosed in the application. Thus, the breadth of the claims also favors a determination that the claims are enabled throughout their full scope by the application as filed.

In summary, it is submitted that for the reasons set forth above, and because the claims are tailored with respect to the breadth of the compounds used in the claimed methods, pending claims 1, 9, 13, 15, and 19-24 fully comply with 35 U.S.C. §112, first paragraph, and that the rejection should be withdrawn.

Claims 1, 2, 4, 7, 9, and 25 stand rejected under 35 U.S.C. §103 as being obvious over WO 01/17976 (WO '976) in view of a Wu publication (Wu). Claims 13-15 and 19-24 stand rejected under 35 U.S.C. §103 as being obvious over WO '976 in view of Wu, and further in view of U.S. Patent No. 6,037,347 ('347). For the reasons set forth below, it is submitted that these rejections are in error and should be withdrawn.

WO '976 is directed to bis-sulfonamides that are asserted to be ET_A and/or ET_B antagonists. In the specification at page 2, lines 5-13, WO '976 discloses numerous disease states wherein plasma and tissue levels of ET-1 are increased, and diseases wherein administration of an endothelin antagonist may provide a benefit. In particular, increased ET-1 levels are found in migraine (page 2, line 8) and an endothelin antagonist may be useful in cerebral vasospasm following subarachnoid hemorrhage (page 2, lines 11-12). No other

cerebral related diseases are disclosed, and these disclosed conditions are in no way related to AD. At page 13, lines 3-14 of WO '976, the reference discloses additional diseases that may be treated by the bis-sulfonamide compounds disclosed in WO '976. Four of the diseases are cerebral ischemia, dementia, migraine, and subarachnoidal hemorrhage. Other diseases are as diverse as cancers, erectile dysfunction, coronary diseases, sepsis, and organ transplant. Alzheimer's disease is neither taught nor suggested.

It is submitted that a person skilled in the art, after reading WO '976 would not make a jump in reasoning and consider using an endothelin antagonist of WO '976, or any other endothelin antagonist, in the treatment of AD. The reference merely lists "dementia" in a laundry list of diverse diseases of different etiologies, with no hint of what these dementias are and which can be treated. As stated by the examiner in supported the rejection under 35 U.S.C. §112, first paragraph, there are many forms of dementia. Accordingly, which dementias are treatable are not disclosed by WO '976.

WO '976 also contains absolutely no teaching or suggestion that Alzheimer's disease can be treated by a disclosed compound. It is the applicant that first conceived and disclosed the use of an endothelin antagonist to treat AD.

It should be noted that Table 1 of WO '976 adds nothing to the WO '976 disclosure with respect to the present claims. The table merely provide IC_{50} values for inhibiting endothelin receptors by the compounds of WO '976. The data shows the relative potency of the bis-sulfonamide compounds in inhibiting endothelin. The data has no relation to using the compounds to treat AD.

The Wu reference does not overcome the deficiencies of WO '976 with respect to using an endothelin antagonist recited in the claims to treat AD in a human. The Wu reference is relied upon for a teaching of various endothelin antagonists, and that bosanten is in clinical trials.

Wu is a review article that teaches, identifies, and classifies various endothelin antagonists. Notably, Wu does *not* teach or suggest the use of an endothelin antagonist in the treatment of AD. At most, Wu suggests use of an endothelin antagonist disclosed therein as

an agent to treat diseases disclosed in WO '976. However, this combination of WO '976 and Wu fails to teach or suggest that an endothelin antagonist can be used to treat a human suffering from AD.

A person skilled in the art, even with the Wu reference before him, still would not have had any apparent reason to make the leaps in reasoning discussed above with respect to WO '976 and thereby arrive at the presently claimed invention. Even a substitution of an endothelin antagonist of Wu into WO '976 would not overcome the deficiencies of WO '976 in rendering the present claims obvious. Furthermore, it is arguable that a person reading Wu, which teaches the treatment of diseases similar to those disclosed in WO '976 (See Wu publication page 1653) would consider using an endothelin antagonist to treat AD.

In summary, in view of the amendments to the claims, and for the reasons set forth above with respect to the patentability of the present claims over WO '976, it is submitted that the present claims are patentable over a combination of WO '976 and the Wu reference. Accordingly, this rejection of claims 1 and 9 under 35 U.S.C. §103 should be withdrawn.

With respect to the rejection of claims 13-15 and 19-24 over a combination of WO '976, Wu, and the '347 patent, the examiner relies upon the '347 patent for a teaching that cholinesterase inhibitors are known to treat dementias. Claims 13-15 and 19-24 recite preferred embodiments of the present invention. However, applicant does not rely upon the administration of a cholinesterase inhibitor to treat AD as the sole point of patentability.

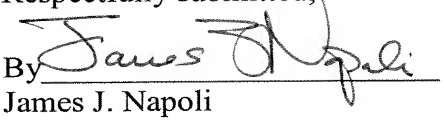
Applicant relies upon all the features recited in claims 13, 15, and 19-24 *and* the claims from which they depend, including claim 1, for patentability. The '347 patent fails to overcome the deficiencies of WO '976 and Wu with respect to treating a human suffering from AD with an endothelin antagonist. Therefore, claims 13-15 and 19-24 are patentable over a combination of WO '976, Wu, and the '347 patent, for the same reasons claims 1 and 9 are patentable over a combination of WO '976 and Wu. Accordingly, the rejection of claims 13, 15, and 19-24 under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are now in a form and scope for allowance. An early and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Dated: October 11, 2007

Respectfully submitted,

By 

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